APPENDIX 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: F. Charles Brunicardi	§	Group Art Unit: 1632
Filed: Sept. 5, 2003	§	Examiner: Sgagias, Magdalene K.
Serial No: 10/656,450	§	Confirmation No.: 8472
For: PROMOTER DRIVEN TISSUE SPECIFIC CYTOTOXIC AGENTS AND METHODS OF USE	§	Publication No. US20050059620

DECLARATION UNDER 37 CFR § 1.132 OF F. CHARLES BRUNICARDI

I, F. Charles Brunicardi, do hereby declare as follows:

I. OVERVIEW OF CREDENTIALS

A. I am over the age of 18 years and am competent to make this declaration.

B. I earned my M.D. in 1980 from the Rutgers School of Medicine, Piscataway, New Jersey, before becoming a Resident and, in 1988, Chief Resident in General Surgery at the State University of New York (SUNY) Health Science Center, Brooklyn. While at SUNY, I received a three-year research fellowship in pancreatic physiology. In 1989, I began a six-year tenure with the UCLA Medical Center in Los Angeles, where, along with my position as Staff Surgeon, I became the Director of the Islet Transplantation Program. In joining in 1995 the faculty of the Baylor College of Medicine, Houston, Texas, I became Director of Human Islet Transplantation, and, from 1999 to 2003, Founder and Director of the Elkins Pancreas Center. Since 1999, I have served as the DeBakey/Bard Professor and Chair of the Michael E. DeBakey Department of Surgery at the Baylor College of Medicine.

C. I have conducted research on the molecular physiology of the endocrine pancreas for well more than twenty years. The molecular biology of pancreatic cancer and other related conditions has been a key area of research interest for me for more than ten years. I have given presentations on gene therapy in many of the more than 25 book chapters and 190 publications that I have authored or co-authored, as well as in many of the more than 270 invited lectures that I have given. Among the more than 20 funded grants for which I have served (or currently

serve) as Principal Investigator, Co-Investigator, Mentor, or Training Faculty Member, the following three funded grants have gene therapy as an emphasis:

1. NIH-NCI-K08-CA76185-04: Adenoviral Based Therapy of Hepatocellular Carcinoma (Mentor), 1998-2003: $426,969.
2. Texas Higher Education Coordinating Board-ARP/Advanced Technology Program: Beta Cell Specific Cytotoxicity Using a Rat Insulin Promoter Thymidine Kinase Construct (Principal Investigator), 2000-2001: $197,744.
3. NIH-NCI-R01-CA95731: Pancreatic Cancer Treatment Using Surgery and Gene Therapy (Principal Investigator), 2002-2007: $1,339,450.

II. GENERAL INFORMATION RELATIVE TO REVIEW

A. I have reviewed: the present above-referenced patent application and its parent (i.e., patent application serial no. 09/686,631, now U.S. Patent No. 6,716,824); the set of claims in the prior Response from the Applicant dated September 2, 2006; the resulting Office Action (Final) from the U.S. Patent and Trademark Office dated November 16, 2006; and the previous Office Action dated March 3, 2006. I have also reviewed the Response (and, in particular, the currently amended claims therein) with which this Affidavit is being filed.

B. In part, the above-noted Office Action (Final) states a rejection of claims 119–139 (i.e., the claims pending before the current amendments) under 35 U.S.C. § 112, first paragraph, for failure to comply with the enablement requirement. In particular concerning enablement, the Office Action (Final) concludes (pages 5) in pertinent part as follows:

> "The breadth of the claims encompass in vivo methods of delivery being for purposes of gene therapy of killing a pancreatic tumor cell in a subject having a pancreatic tumor. For the reasons presented in the office action mailed 3/3/06, the rejection over methods of delivery in vivo are maintained as not being enabled because at the time of filing gene therapy was regarded by the art as being unpredictable without undue experimentation. The Hardy paper cited by the Applicant provides evidence for the construction of and production of highly enriched gutless adenovirus based vector preparation in very large quantities for gene therapy. However, the Hardy paper does not provide evidence to override the issue of unpredictability of administering to a subject having a pancreatic tumor a vector comprising said cytotoxic gene wherein the gene is expressed at sufficient levels and administering a prodrug to said subject resulting in killing a pancreatic tumor cell in a subject."

C. As summarized further above, I am recognized as having significant expertise in gene therapy for the periods before and after the filing date of parent patent application serial no. 09/686,631 (now U.S. Patent No. 6,716,824) (i.e., October 11, 2000).

D. I believe I am qualified to give a relevant opinion on the enablement of the currently amended claims.

III. THE PRESENT APPLICATION ENABLES PENDING CLAIMS 119–153

A. Baylor College of Medicine is a leading institution in developing suicide gene therapy for cancer. The pioneering work in suicide gene therapy was performed at the Baylor College of Medicine by Dr. Savio Woo, an inventor on the basic suicide gene therapy patents (see U.S. Patent Nos. 6,217,860 "Gene therapy for solid tumors, papillomas and warts"; 6,066,624 "Gene therapy for solid tumors using adenoviral vectors comprising suicide genes and cytokine genes"; and 5,631,236 "Gene therapy for solid tumors, using a DNA sequence encoding HSV-Tk or VZV-Tk"). The filing date of the patent application that issued as U.S. Patent No. 6,217,860 (i.e., September 24, 1999) precedes the October 11, 2000 filing date of parent patent application serial no. 09/686,631 (now U.S. Patent No. 6,716,824) by more than one year, and the issue dates of U.S. Patent Nos. 6,066,624 and 5,631,236 precede that filing date by more than 4 months and more than 40 months, respectively.

B. Scientific publications from before the October 11, 2000 filing date of parent patent application serial no. 09/686,631 enable suicide gene therapy, as evidenced by scientific publications showing safety and some efficacy in phase 1 and 2 clinical trials. For example, Shalev and colleagues review a phase I clinical study and three then open clinical trials of prostate cancer suicide gene therapy in their April 2000 paper [see pages 127–128 of attached Shalev et al., "Suicide gene therapy for prostate cancer using a replication-deficient adenovirus containing the herpesvirus thymidine kinase gene," *World J. Urol.* 18 (2): 125–129 (2000)]. They note a lowering of vector doses to below 1 X 10^{10} IU for safety, and they conclude that this clinical research showed both safety and some efficacy [i.e., "The HSV-tk/GCV regimen has proved to be safe, even for multiple and repeated injections, and to have some efficacy."]. This research also demonstrates that SCID mice data, as also disclosed in the present application, is applicable to human clinical studies.

C. Scientific publications from before the October 11, 2000 filing date of parent patent application serial no. 09/686,631 also enable liposomal delivery of cytotoxic genes in suicide gene therapy for cancer. For example, Nagamachi and colleagues constructed a model of metastatic non-small cell lung cancer (NSCLC) by injected human NSCLC cell lines into

BALB/c nude mice. Using this model, they provide evidence of the therapeutic feasibility of an *in vivo* lipofection-based suicide gene therapy (i.e., thymidine kinase gene injection intrapleurally as a DNA-liposome complex before ganciclovir administration) for lung cancer pleural metastasis [see attached Nagamachi et al., "Suicidal gene therapy for pleural metastasis of lung cancer by liposome-mediated transfer of herpes simplex virus thymidine kinase gene," *Cancer Gene Ther.* 6 (6): 546–53 (1999)]. As another pertinent example, Aoki and colleagues constructed a model of pancreatic cancer by inoculating human PSN-1 pancreatic cancer cells into the peritoneal cavity of nude mice. Using this model, they provide evidence of the therapeutic feasibility of an *in vivo* (intraperitoneal) lipofection-based suicide gene therapy (thymidine kinase gene injection as a DNA-lipoployamine complex before ganciclovir administration) for treating pancreatic cancer [see attached Aoki et al., "Gene therapy for peritoneal dissemination of pancreatic cancer by liposome-mediated transfer of herpes simplex virus thymidine kinase gene," *Human Gene Ther.* 8 (9): 1105–13 (1997); not only is the Aoki et al. disclosure directed to lipofection-based suicide gene therapy of pancreatic cancer, but the Aoki et al. publication date (i.e., June 10, 1997) precedes the October 11, 2000 filing date of parent patent application serial no. 09/686,631 by more than 40 months].

D. Scientific publications from before the October 11, 2000 filing date of parent patent application serial no. 09/686,631 also enable adenoviral delivery of cytotoxic genes for suicide gene therapy of cancer. For example, Block and colleagues at the Baylor College of Medicine reported on adenovirus-mediated suicide gene therapy directed against intrahepatic tumors generated by inoculation of murine pancreatic cancer cells into the left lateral liver lobe of mice [see attached Block et al., "Adenoviral-mediated herpes simplex virus thymidine kinase gene transfer: regression of hepatic metastasis of pancreatic tumors," *Pancreas* 15 (1): 25–34 (1997)]. Injection of the tumor with a thymidine kinase construct followed by intraperitoneal ganciclovir application caused significant tumor volume reduction and necrosis. As another pertinent example, Makinen and colleagues found that, in *in vivo* HSV-TK-transduced pancreatic tumors, ganciclovir treatment caused tumor necrosis in an immunocompetent animal model [see attached Makinen et al., "Evaluation of herpes simplex thymidine kinase mediated gene therapy in experimental pancreatic cancer," *J. Gene Med.* 2 (5): 361–367 (2000); paper published online May 26, 2000].

E. In consideration of the foregoing evidence, as well as extensive related evidence (particularly directed to the high level of skill in the art, as well as multiple enabling aspects of the prior art), my conclusion is that the present application enables pending claims 119–153.

* * * * *

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: 5/16/07

F. Charles Brunicardi

F. Charles Brunicardi, M.D., F.A.C.S.